

REMARKS

Claims 6-8, 10-22, and 25-28 are pending in the instant application. No new matter has been added as a result of the above-described amendments. Support for the amendments can be found in the specification at, for example, page 17, lines 1-6. The rejections set forth in the Office Action are traversed by argument below.

1. Rejections of claims 6-8, 10-22, and 25-28 under 35 U.S.C. § 112, first paragraph

The Office Action asserts a rejection of claims 6-8, 10-22, and 25-28 under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Action states that while claim 25, as amended in Applicants' response to the Office Action mailed August 14, 2001, is directed to a KGF-2 protein consisting of residues 66 through 208 of the amino acid sequence set forth in SEQ ID NO: 2, or a KGF-2 protein consisting of residues 66 through 208 of the amino sequence set forth in SEQ ID NO: 2 and an N-terminal methionine, the as-filed specification does not disclose a KGF-2 protein consisting of residues 66 through 208 of the amino acid sequence set forth in SEQ ID NO: 2. The Action also states that while Applicants indicate in their response to the Office Action mailed August 14, 2001 that the KGF-2 protein consisting of residues 66 through 208 of the amino sequence set forth in SEQ ID NO: 2 and the disclosed variant dN29 FGF-10 describe identical proteins, the specification discloses that Figure 2 depicts the amino acid sequence of dN29 FGF-10, which is identical to residues 69 through 208 – rather than 66 through 208 – of the amino sequence set forth in SEQ ID NO: 2.

Applicants respectfully disagree with the Action's assertion that the as-filed specification does not disclose a KGF-2 protein consisting of residues 66 through 208 of the amino acid sequence set forth in SEQ ID NO: 2. Claim 25, as originally presented in Applicants' response filed September 11, 2000, recited a KGF-2 protein consisting of the amino acid sequence NH₂-His-Val-Arg-Ser-Tyr-[Asn⁷¹-Ser²⁰⁸]-COOH or the amino sequence NH₂-His-Val-Arg-Ser-Tyr-[Asn⁷¹-Ser²⁰⁸]-COOH also having an N-terminal methionine. As noted in the instant Action, Applicants amended claim 25 in their response to the Office Action mailed August 14, 2001 to replace the term "NH₂-His-Val-Arg-Ser-Tyr-[Asn⁷¹-Ser²⁰⁸]-COOH," which was inconsistent with 37 C.F.R. §§ 1.821(b) and

(d) and 1.822(d), with the term “residues 66 through 208 of the amino acid sequence set forth in SEQ ID NO: 2,” which is consistent with M.P.E.P. § 2423.03. Applicants contend that both terms describe the *same* KGF-2 variant.

Applicants first wish to direct the Examiner’s attention to page 18, lines 6-8 of the specification, where Applicants teach a KGF-2 variant having the amino acid sequence NH₂-His-Val-Arg-Ser-Tyr-[Asn⁷¹-Ser²⁰⁸]-COOH. Applicants also note that the instant specification teaches that (a) Figure 1 and SEQ ID NO: 2 depict the full-length amino acid sequence of recombinant human KGF-2 (page 5, lines 25-26), (b) the initial 36 amino acid residues (*i.e.*, Met¹ to Thr³⁶) of sequence depicted in Figure 1 and SEQ ID NO: 2 represent the putative leader sequence of full-length KGF-2 (page 5, lines 26-28), and (c) the term “[Asn⁷¹-Pro²⁰³],” for example, represents residues 71 through 203 of SEQ ID NO: 2 (page 15, lines 14-15). Exhibit A shows the amino acid sequence of SEQ ID NO: 2, with the putative leader sequence indicated by double-underlining, the residues at positions 66-70 (*i.e.*, His-Val-Arg-Ser-Tyr) indicated by bold underlining, and the residues at positions 71-208 (*i.e.*, [Asn⁷¹-Ser²⁰⁸]) indicated by underlining. Applicants contend that Exhibit A clearly illustrates that the terms “NH₂-His-Val-Arg-Ser-Tyr-[Asn⁷¹-Ser²⁰⁸]-COOH” and “residues 66 through 208 of the amino acid sequence set forth in SEQ ID NO: 2” are merely alternative expressions for the *same* amino acid sequence, and that the explicit recitation of the amino acid sequence NH₂-His-Val-Arg-Ser-Tyr-[Asn⁷¹-Ser²⁰⁸]-COOH in the as-filed specification provides support for a KGF-2 protein consisting of residues 66 through 208 of the amino acid sequence set forth in SEQ ID NO: 2.

Applicants next address the Action’s assertion that the disclosed variant dN29 FGF-10 and the KGF-2 protein consisting of residues 66 through 208 of the amino sequence set forth in SEQ ID NO: 2 do not describe identical proteins. Applicants agree that the variant described in Example 3 is dN29 hFGF10 rather than ΔN29 KGF-2, and therefore, the variant described in Example 3 consists of residues 69 through 208 of the amino sequence set forth in SEQ ID NO: 2 rather than residues 66 through 208. Applicants, however, contend that because the dN29 hFGF10 variant, which is three amino acids shorter than the ΔN29 KGF-2 variant, was found to exhibit proliferative activity in a Balb/MK mouse keratinocyte proliferation assay (*see* Example 2), one of ordinary skill in the art would expect the slightly longer ΔN29 KGF-2 variant to also exhibit the proliferative activity of

mature KGF-2. Moreover, as Applicants noted in their response to the Office Action mailed August 14, 2001, the *Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, P1, "Written Description" Requirement* ("*Guidelines*") do not require that Applicants show an actual reduction to practice in cases such as this one. Rather, the *Guidelines* merely state that:

[D]escribing an actual reduction to practice is one of a number of ways to show possession of the invention. ... Actual reduction to practice may be crucial in the relatively rare instances where the level of knowledge and level of skill are such that those of skill in the art cannot describe a composition structurally, or specify a process of making a composition by naming components and combining steps, in such a way as to distinguish the composition with particularity from all others.

Guidelines, 66 Fed. Reg. 1099, 1101 (2001). Applicants, therefore, respectfully submit that claims 6-8, 10-22, and 25-28 satisfy the requirements of 35 U.S.C. § 112, first paragraph, in that Applicants had possession of the claimed invention, and request that this ground of rejection be withdrawn.

The Office Action also asserts a rejection of claims 6-8, 10-22, and 25-28 under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention. The Action states that because the specification as filed does not provide any guidance or working examples regarding a keratinocyte growth factor-2 protein consisting of residues 66 through 208 of the amino acid sequence set forth in SEQ ID NO: 2, and the art is silent with respect to this protein, and because of the complex nature of the invention, and the unpredictability of mutation on protein structure and function, it would require undue experimentation for a skilled artisan to make and use the claimed invention.

Applicants understand that the underlying basis for this rejection is the Patent Office's belief that the claimed KGF-2 variant was not described in the as-filed specification. Applicants respectfully submit that they have traversed this misunderstanding in their response to the written description rejection set forth above, and further contend that, once the Patent Office appreciated Applicants' disclosure of the claimed variant, the Office will appreciate that the instant specification is enabling for the disclosed variant. In addition, and as discussed in Applicants' response to the Office Action mailed August 14, 2001, the instant specification teaches several pharmaceutically and physiologically acceptable vehicles that can be combined with the KGF-2 protein of the invention to

form a suitable pharmaceutical composition (page 43, line 29 to page 46, line 21); procedures for determining acceptable dosages for use in administering the pharmaceutical compositions of the invention (page 47, line 10 to page 48, line 8); that because the KGF-2 proteins of the invention can be used, *inter alia*, to modulate epithelial cell proliferation in the gastrointestinal tract, the KGF-2 proteins of the invention are useful for treating or preventing diseases and disorders of the gastrointestinal tract (page 54, line 5 to page 61, line 4); that a pharmaceutical composition comprising the dN29 hFGF10 variant and a pharmaceutically acceptable vehicle is effective in preventing chemotherapy-induced pulmonary fibrosis in rats (Example 3), and that the dN29 hFGF10 variant retains KGF-2 activity in a murine keratinocyte proliferation assay (Example 2). Applicants contend, therefore, that in view of the teachings of the instant specification, one of ordinary skill in the art would know how to make and use the claimed invention. Applicants further contend that based on the teaching in the instant specification that a slightly shorter truncation KGF-2 variant retains KGF-2 activity in a murine keratinocyte proliferation assay, it would not require undue experimentation for a skilled artisan to make and use the claimed invention. Applicants, therefore, respectfully request that this ground of rejection be withdrawn.

Applicants respectfully contend that rejections based on 35 U.S.C. § 112, first paragraph, have been traversed by argument, and request that the Examiner withdraw all rejections made on this basis.

CONCLUSIONS

Applicants respectfully contend that all conditions of patentability are met in the pending claims as amended. Allowance of the claims is thereby respectfully solicited.

If Examiner Kemmerer believes it to be helpful, she is invited to contact the undersigned representative by telephone at 312-913-0001.

Respectfully submitted,
McDonnell Boehnen Hulbert & Berghoff

Dated: September 19, 2003

By:

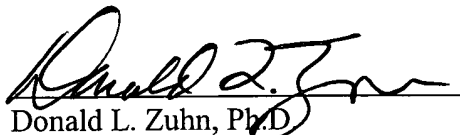

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EXHIBIT A

Met	Trp	Lys	Trp	Ile	Leu	Thr	His	Cys	Ala	Ser	Ala	Phe	Pro	His	Leu
1				5					10					15	
Pro	Gly	Cys	Cys	Cys	Cys	Cys	Phe	Leu	Leu	Leu	Phe	Leu	Val	Ser	Ser
			20					25					30		
Val	Pro	Val	Thr	Cys	Gln	Ala	Leu	Gly	Gln	Asp	Met	Val	Ser	Pro	Glu
		35					40					45			
Ala	Thr	Asn	Ser	Ser	Ser	Ser	Ser	Phe	Ser	Ser	Pro	Ser	Ser	Ala	Gly
	50						55				60				
Arg	His	Val	Arg	Ser	Tyr	Asn	His	Leu	Gln	Gly	Asp	Val	Arg	Trp	Arg
65					70					75					80
Lys	Leu	Phe	Ser	Phe	Thr	Lys	Tyr	Phe	Leu	Lys	Ile	Glu	Lys	Asn	Gly
				85					90					95	
Lys	Val	Ser	Gly	Thr	Lys	Lys	Glu	Asn	Cys	Pro	Tyr	Ser	Ile	Leu	Glu
			100					105					110		
Ile	Thr	Ser	Val	Glu	Ile	Gly	Val	Val	Ala	Val	Lys	Ala	Ile	Asn	Ser
		115					120					125			
Asn	Tyr	Tyr	Leu	Ala	Met	Asn	Lys	Lys	Gly	Lys	Leu	Tyr	Gly	Ser	Lys
	130						135				140				
Glu	Phe	Asn	Asn	Asp	Cys	Lys	Leu	Lys	Glu	Arg	Ile	Glu	Glu	Asn	Gly
145					150					155					160
Tyr	Asn	Thr	Tyr	Ala	Ser	Phe	Asn	Trp	Gln	His	Asn	Gly	Arg	Gln	Met
				165					170					175	
Tyr	Val	Ala	Leu	Asn	Gly	Lys	Gly	Ala	Pro	Arg	Arg	Gly	Gln	Lys	Thr
			180					185					190		
Arg	Arg	Lys	Asn	Thr	Ser	Ala	His	Phe	Leu	Pro	Met	Val	Val	His	Ser
		195					200					205			